

Combination Microbicides Protect Monkeys Against HIV-Like Virus

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Experiments in female monkeys have for the first time shown that when used in combination, vaginal gels known as microbicides can protect against an HIV-like virus. The research, funded largely by the National Institute of Allergy and Infectious Diseases (NIAID), one of the National Institutes of Health (NIH), suggests that similar combination microbicides could potentially provide a safe, effective and practical way to prevent HIV transmission to women, according to study investigators.

The study, published online October 30 in the journal *Nature*, represents the first successful testing of combination microbicides in a primate model.

Women make up nearly half of all people living with HIV worldwide, and a vast majority of new cases of HIV infection in women result from heterosexual intercourse. "This study demonstrates that combination microbicides are feasible," says NIAID Director Anthony S. Fauci, M.D. "We need to build on these promising animal studies and move toward establishing the safety and effectiveness of combination microbicides in women."

Vaginal microbicides include creams, gels or other substances that could be applied topically to prevent the transmission of HIV and other sexually transmitted infections. At least five different candidate microbicides currently are being evaluated in large clinical trials, but no microbicide has yet been approved for human use.

The *Nature* study was led by John P. Moore, Ph.D., of the Weill Medical College of Cornell University in New York City, and Ronald S. Veazey, D.V.M., Ph.D., of the Tulane National Primate Research Center in Covington, LA. For the experiments, they used simian-human immunodeficiency virus (SHIV), a hybrid virus made in the laboratory from HIV and its cousin, SIV, which infects only non-human primates. The researchers tested three microbicide gels alone and in combination. Two contained small molecules and the third featured a modified assembly of protein building blocks; each of the three was designed to block SHIV from entering specific cells in the vaginal area and thereby prevent the virus from invading the monkey's body. The two small molecules were provided by Bristol Myers Squibb Inc. (BMS), based in Wallingford, CT, and Merck Research Laboratories, headquartered in Rahway, NJ. Weill Cornell Medical College supplied the third compound, which is similar to the approved anti-HIV drug Enfuvirtide (Fuzeon).

During testing, researchers sedated the monkeys, applied the experimental gels, and exposed the animals to a single virus dose 30 minutes to 12 hours later.

Each of the three microbicide gels provided protection against the virus when used alone. Moreover, of the 20 monkeys given the BMS and Merck microbicides in combination, 16 were protected from infection. All three monkeys given the triple combination of microbicides remained virus-free. None of the monkeys appeared to experience vaginal irritation or inflammation from the experimental gels. Of note, the researchers found that the Merck and BMS compounds could be applied up to six hours prior to exposure to the virus and still offer protection.

"This is encouraging for the development of a microbicide for use in the real world," says Dr. Moore. Jim Turpin, Ph.D., of NIAID's Topical Microbicide Team, says, "Just as we've seen with combination antiviral medicines, this study shows that if you can hit two or more different targets of the virus, the greater the effectiveness of the product."

The research team deliberately chose the three specific test compounds for several reasons. "We felt these inhibitors were likely to be fairly safe," says Dr. Veazey. "Similar compounds have a good safety record in humans thus far."

The small molecules were also chosen for their potential as a cost-effective product for women. "A microbicide has to be safe, effective and socially acceptable, but the cost of its active ingredients will also be an issue," says Dr. Moore. "We didn't want to work with inhibitors that could not be made in large quantities or would be produced only at great expense. Instead, we selected compounds similar to those now being developed as antiviral drugs for treating HIV-1 infection because we thought they might be practical to develop as a microbicide."

Although encouraged by their findings, Dr. Moore notes, "Animal studies are an important step, but there is much more work that needs to be done before a product can be made available for human use. Small clinical trials to determine safety and optimal dosage will be the next stage."

NIAID is a component of the National Institutes of Health, an agency of the U.S. Department of Health and Human Services. NIAID supports basic and applied research to prevent, diagnose and treat infectious diseases such as HIV/AIDS and other sexually transmitted infections, influenza, tuberculosis, malaria and illness from potential agents of bioterrorism. NIAID also supports research on transplantation and immune-related illnesses, including autoimmune disorders, asthma and allergies.

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Reference: RS Veazey *et al.* Protection of macaques from vaginal SHIV challenge by vaginally delivered inhibitors of virus-cell fusion. *Nature* DOI:10.1038/nature04055 (2005)

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